REMARKS

I. The Subject Matter of the Claims

In general, the subject matter of the claims relates to monoclonal antibodies specifically reactive with α_d integrin which also modulate TNFα activity. The foregoing amendment is in the revised amendment format as provided in 1267 OG 106. Accordingly, the provisions of 37 C.F.R. § 1.21, requiring submission of clean and marked-up versions of the replacement paragraphs and claims, are waived.

II. The Objections to the Specification

Applicants note the Examiner's objection in paragraph 4 regarding the formal drawings and will submit final drawings upon notification of allowance.

III. Amendments

Support for the amendment to claim 11 and 12 can be found at page 17, lines 2-4 which describes an anti-α_d antibody which inhibits TNFα release.

IV. Patentability Arguments

A. The Rejection of Claims 11-14 under 35 U.S.C. §112 First Paragraph, May Properly be Withdrawn

In paragraph 6 of the Office Action, the Examiner rejects claims 11-14 under 35 U.S.C. §112, first paragraph, as assertedly not being enabled by the specification for "any α_d specificity as the target of the claimed methods." The Examiner contends that the specification does not enable any α_d that hybridizes to the complement of the polynucleotide of claim 11(a) or (b). The Examiner alleges that Applicants have not provided sufficient structural and functional attributes of the α_d molecule to enable <u>any</u> α_d.

Applicants respectfully disagree. Contrary to the Examiner's assertion, the specification describes several functional characteristics which allow the worker of skill in the art to obtain an α_d polypeptide as taught herein, and therefore, monoclonal antibodies immunoreactive with these α_d polypeptides.

Regarding functional properties, example 12, at page 41, lines 21-29, of the specification discloses functional properties of α_d binding. The specification teaches that α_d/CD18 binds to ICAM-R with 3-5 fold greater affinity than control protein (BSA). The specification also discloses that CD11a/CD18 binds ICAM-1, while α_d/CD18 does not bind ICAM-1, demonstrating that α_d exhibits unique properties compared to other integrin alpha subunits. Page 42, lines 10-24, of the specification teach that 40-50% of α_d-transfected cells bind to ICAM-R and none of these cells bind ICAM-1, and this binding pattern is distinct from that observed with CD11a and CD11b. Assessment of ICAM-R ligand binding, using antibodies that bind specific ICAM-R domains, shows that α_d binds ICAM-R within a different domain than CD11a. The specification further discloses, at page 44, lines 7-8, that the α_d polypeptide does not bind to a mutant ICAM-R. Thus, α_d is readily identified based on its ability to bind ICAM-R, its affinity for binding ICAM-R, and the region of ICAM-R it binds compared to other ligands.

Moreover, page 43, lines 13-21, of the specification demonstrates that α_d binds VCAM-1, and compares the rate of α_d/VCAM-1 binding with VCAM-1 binding to control protein or E-selectin. The specification also indicates that α_d/VCAM-1 binding is partially blocked by an antibody to the first domain of VCAM-1, thereby functionally describing where in the VCAM-1 protein α_d may bind.

Additional examples describing α_d binding to its binding partners may be found at, for instance, page 43, lines 7-11; page 43, lines 21-24; and page 158, lines 20-30 which describe the binding of α_d to specific VCAM-1 domains. Thus, the specification discloses numerous functional properties of α_d that a worker of skill could use, without undue experimentation, to obtain an α_d molecule used in the methods of the invention.

The specification also discloses numerous structural properties of α_d which enable one of skill in the art carry out the claimed invention. For example, several other α_d molecules, including human α_d variants (SEQ ID NO: 96-99) and α_d from other species (e.g. dog, rat, mouse, rabbit), are disclosed which are shown to hybridize to α_d of SEQ ID NO: 1 (see Page 33, lines 14-20 and Table 1, page 121). These α_d molecules were isolated using techniques commonly practiced in the art with primers and hybridization probes described in the specification, for example, in Example 28, at page 105, lines 29-30 and page 109, lines 4-15.

Applicants proposed to isolate α_d-hybridizing molecules, readily isolated several clones, and identified them as α_d molecules using the functional characteristics described above.

Additional structural comparisons with related integrins (see page 31, lines 8-13) indicate that the cytoplasmic region of α_d differs markedly from that of CD11a, CD11b or CD11c, suggesting that an α_d polynucleotide or polypeptide would not share high homology with other CD11 molecules. Table 1, page 121, shows that other CD18 binding partners, CD11a, CD11b, and CD11c, which do not share many functional characteristics with α_d, demonstrate low amino acid homology with α_d. However, sequences with higher amino acid homology to α_d, e.g. orthologous α_d molecules, are shown to hybridize with α_d set out in SEQ ID NO: 1, and also share nearly identical functional properties.

Any α_d-encoding molecule identified to hybridize to the polynucleotide of SEQ ID NO: 1 or to a polynucleotide encoding the polypeptide of SEQ ID NO: 2, thus sharing structural properties of α_d, are then assessed for their functional properties (e.g. ICAM-R or VCAM-1 binding, lack of ICAM-1 binding, blockade of binding by specific antibodies), which identify a molecule as an α_d molecule. These functional properties are well-described in the specification and a worker of skill would not require undue experimentation to obtain a molecule that hybridizes with α_d as set forth in the claims, and having the functional properties of an α_d molecule. As such, Applicants submit that the rejection of claims 11-14 under 35 U.S.C. §112, first paragraph, as lacking enablement, may properly be withdrawn.

B. The Rejection of Claims 11-14 under 35 U.S.C. §112, Second Paragraph, May Properly be Withdrawn

In paragraph 7, the Examiner asserts that claims 11-14 are indefinite in their recitation of the term "modulating." Applicants contend that "modulating" is clearly defined in the specification at page 19, line 8, to be either the inhibition or enhancement of a particular activity (in the instant case, TNF-α activity).

However, in order to advance prosecution of the application, Applicants have amended claims 11 and 12 to recite a method for inhibiting TNF-α release. as suggrested by the Examiner. Support for this amendment is found at page 17, lines 2-4, which describes an anti-α_d antibody which inhibits TNFα release.

C. The Rejection of Claims 11-14 under 35 U.S.C. §102(b), May Properly be Withdrawn.

In paragraph 8 the Examiner rejects claims 11-14 under 35 U.S.C. §102(b) for assertedly being anticipated by Gallatin, which allegedly teaches methods of treating immune or inflammatory responses with antibodies to α_d.

Applicants respectfully disagree. The present invention involves methods for specifically modulating TNFα activity using monoclonal antibodies to α_d, and Gallatin neither discloses nor suggests any ability of α_d-specific antibodies to modulate TNFα activity. Gallatin simply describes a method for producing α_d-specific antibodies and discloses a general use for the disclosed antibodies for treating immune or inflammatory responses, without characterizing functional properties of any particular of α_d-specific monoclonal antibodies or methods for their use. The Examiner contends, however, that modulation of TNFα activity is an inherent property of the antibodies disclosed by Gallatin.

For a reference to anticipate, that single reference must disclose each and every limitation of the claimed invention. Further, MPEP 2131.01 (III) states that to serve as anticipatory art when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill (*emphasis added*).

A worker of skill might predict from the disclosure of Gallatin that a monoclonal antibody that blocks α_d binding to a receptor might modulate the inflammatory response by inhibiting accumulation or migration of cell types expressing α_d (e.g. leukocytes) to the site of inflammation. The blockade of ligand binding by an antibody is an extracellular event that a worker of skill might expect to take place given the specificity of an antibody. The present invention, however, is directed to the regulation of an intracellular event, TNFα expression, which one of ordinary skill would not necessarily expect when using an antibody to block binding to an extracellular molecule. For instance, example 41, page 151-152, shows that administering anti- α_d monoclonal antibody to an isolated population of cells, splenic phagocytes, does not modulate their migration to a site of inflammation, but modulates TNFα expression. This suggests that there is an intracellular response to monoclonal antibody binding

that would not have been expected simply by reading Gallatin. The modulation of cell migration to a site of inflammation by α_d antibodies and the modulation of intracellular events are two different principles of inflammatory regulation by α_d antibodies that would not necessarily be recognized by a worker of skill, given the level of knowledge of α_d at the time of Gallatin.

Thus, nothing in the disclosure of Gallatin suggests, nor would it have been so recognized by a person of ordinary skill at the time of filing of Gallatin, that an anti-α_d antibody would have any effect on intracellular macrophage activity, especially the modulation of TNFα activity. As such, Applicants submit that the rejection of claims 11-14 under 35 U.S.C. § 102(b) should properly be withdrawn.

D. The Rejection of Claims 11-14 under the Doctrine of Obviousness-type Double Patenting May Properly be Withdrawn.

In paragraph 15 of the Office Action, the Examiner rejects claims 11-14 based on non-statutory obviousness-type double patenting as allegedly unpatentable over claims 1-10 of U.S. Patent No. 6,251,395 (hereinafter "the '395 patent") and claims 1-9 of U.S. Patent No. 6,432,404 (hereinafter "the '404 patent"). The Examiner states that the subject matter of the currently pending claims, which are directed to modulating TNFα activity using α_d-specific antibodies, would be an inherent property of the patented methods, directed to inhibiting inflammation in central nervous system (CNS) injury by administration of α_d antibodies, and promoting locomotor recovery/inhibiting locomotor damage following spinal cord injury.

Applicant submits that an objection of obviousness-type double patenting of claims 11-14 as unpatentable over U.S. Patent No. 6,251,395 is inappropriate pursuant to 35 U.S.C. § 121. The present application is a divisional application of serial number 09/193,043, now U.S. Patent No. 6,251,395, and was filed based on a restriction requirement in 09/193,043. 35 USC § 121 states, in part:

> A patent issued on an application with respect to which a requirement for restriction under this section has been made, or on an application filed as a result of such a requirement, shall not be used as a reference either in the Patent and Trademark Office or in the courts against a divisional application...if the divisional application is filed before the issuance of the patent on the other application.

The present application was filed on June 26, 2001, the date of issue of 6,251,395, thereby rendering the '395 patent unavailable as a reference against the present application.

Non-statutory obviousness-type double patenting requires comparison of the application claims and cited patent claims on a claim by claim basis. Use of the specification and all it discloses is improper except to establish a meaning for a claim term. See *In re Boylan* 392 F.2d 1017, 157 USPQ 370 (CCPA 1968). MPEP 804 states that non-statutory type double patenting is primarily intended to prohibit issuance of claims in a second patent not patentably distinguishable from claims in a first patent. A worker of skill in the art looking at the claims of U.S. Patent No. 6,432,404 would not realize that the subject matter of the claims would embrace the modulation of TNFα activity.

The '404 patent claims recite methods for promoting locomotor recovery or inhibiting locomotor damage in the CNS using antibodies to α_d. Many activities promote locomotor recovery or inhibit locomotor damage following spinal cord injury which may be mediated by macrophages, neutrophils or any other cell type that expresses α_d. Inhibition of these cells from infiltrating the CNS could alter expression of inflammatory cytokines, expression of free radicals, and expression of monocyte matrix metalloproteinases, which have been associated with inflammation (Goussev et al., *J Neurosurg.* 99(2 Suppl):188-97. 2003; Zheng et al., *Eur. Respir. J.* 20:170-6; 2003; abstracts submitted herewith).

The present claims are directed to modulation of TNFα from macrophages, whereas the inhibition of locomotor damage claimed in the '404 patent may involve neutrophils, macrophages or any other cell species which may express α_d. As such, it is not obvious to a worker of skill having read the claims in the '404 patent that the modulation of TNFα from macrophages by anti- α_d antibodies is responsible for promoting locomotor recovery or inhibiting locomotor damage in spinal cord injury, as would be required to meet the standard of double patenting. Thus, the claims of U.S. Patent 6,432,404 cannot render the currently pending claims obvious, and the obviousness-type double patenting rejection should properly be withdrawn.

V. Conclusion

In view of the amendments and remarks made herein, Applicants submit that claims 11-14 are in condition for allowance and respectfully request expedited notification of the same.

Respectfully submitted,

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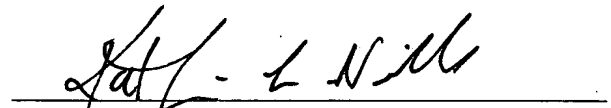
By: 

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1: Eur Respir J. 2002 Jul;20(1):170-6.

Overexpression of matrix metalloproteinase-8 and -9 in bronchiectatic airways in vivo.

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The progressive bronchial dilatation in bronchiectasis is likely to be the resul of continued airway matrix destruction, although little is known about the role of neutrophil matrix metalloproteinases (MMPs) in this process. Immunohistochemistry has been used to investigate the expression and cellular localisation of MMP-8 and MMP-9 in bronchiectatic airways in vivo Endobronchial biopsies were taken from 25 bronchiectatic patients, and from the right lower lobe in 14 control subjects. MMP-8, MMP-9, neutrophils and macrophages were stained with monoclonal antibodies and quantified as positive cell x mm(-2) of the lamina propria by using an image analysis system. There were significantly higher densities of MMP-8 and MMP-9 positive cells in the lamina propria of bronchiectatic than control airways. In bronchiectatic airways, the densities of MMP-8 and MMP-9 positive cells correlated with each other and with neutrophil density, but not with macrophage density. In control airways, a significant correlation was found between MMP-8 with neutrophil and MMP-9 with macrophage densities. An overexpression of neutrophil matrix metalloproteinases in bronchiectatic airways could help explain the continuation of airway destruction in bronchiectasis. In view of the clinical availability of matrix metalloproteinase antagonists, the results presented here could have a significant impact on the development of novel therapies of this untreatable disease.

PMID: 12166566 [PubMed - indexed for MEDLINE]

1: J Neurosurg. 2003 Sep;99(2 Suppl):188-97. Related Articles, Link

Differential temporal expression of matrix metalloproteinases after spinal cord injury: relationship to revascularization and wound healing.

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OBJECT: Matrix metalloproteinases (MMPs), particularly MMP-9/gelatinase B, promote early inflammation and barrier disruption after spinal cord injury (SCI). Early blockade of MMPs after injury provides neuroprotection and improves motor outcome. There is recent evidence, however, that MMP-9 and MMP-2/gelatinase A participate in later wound healing in the injured cord. The authors therefore examined the activity of these gelatinases during revascularization and glial scar formation in the contused murine spinal cord. METHODS: Gelatinase activity was evaluated using gelatin zymography 24 hours after a mild, moderate, or severe contusion injury. The active form of MMP-2 was not detected, whereas MMP-9 activity was evident in all SCI groups and rose with increasing injury severity. The temporal expression of gelatinases was then examined using gelatin zymography after a moderate SCI. The active form of MMP-9 was most prominent at 1 day, extended through the early period of revascularization, and returned to control by 14 days. The active form of MMP-2 appeared at 7 days postinjury and remained elevated compared with that documented in sham-treated mice for at least 21 days. Increased MMP-2 activity coincided with both revascularization and glial scar formation. Using in situ zymography, gelatinolytic activity was detected in the meninges, vascular elements, glia, and macrophage-like cells in the injured cord. Results of immunolabeling confirmed the presence of gelatinase in vessels during revascularization and in reactive astrocytes associated with glial scar formation. CONCLUSIONS: These findings suggest that although MMP-9 and -2 exhibit overlapping expression during revascularization, the former is associated with acute injury responses and the latter with formation of a glial scar.

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